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EXTREME HYPOTHERMIA INDUCED BY A SYNERGISM OF ACUTE LIMBIC SEIZURES, PHYSICAL RESTRAINT, AND ACEPROMAZINE: IMPLICATIONS FOR SURVIVAL FOLLOWING BRAIN INJURY[1,2]

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Summary.—Core temperature was measured in rats 24 hr. after they had been assigned to one of 8 groups in a 3-way analysis of variance design that involved (1) induction of limbic seizures by a systemic injection of lithium/pilocarpine, (2) physical restraint, and (3) administration of acepromazine. An extraordinarily powerful interaction was noted among seizures, physical restraint, and acepromazine-produced hypothermia (24° C) compared to the other 7 treatments (>35° C). The putative poikilothermic response is commensurate with the loss of mammalian behaviors that follow these seizures. Implications for survival during the acute stages of brain injury are suggested.

Systemic injection of lithium chloride (3 mEq/kg) followed 4 hr. later by (subcutaneous injection of) the acetylcholine muscarinic agonist pilocarpine (30 mg/kg) produces protracted limbic seizures that result in mortality within about 24 hr. We have found that subcutaneous injection (30 min. after the pilocarpine) of acepromazine (25 mg/kg) reduces the mortality to less than 20%. While pursuing the psychoneurological mechanisms (Bureau & Persinger, 1991) of the sudden cardiac death that accompanies limbic (complex partial) seizures, we observed an extraordinary synergistic effect upon core body temperature; it was reflected as an interaction between occurrence of seizures, acepromazine, and body restraint.

The experimental design involved a three-way analysis of variance (no seizure, seizure; no acepromazine, acepromazine; no restraint, restraint). A total of 35 male rats (*M* weight: 540 gm; *SD*: 89 gm) were randomly assigned to each of the eight groups (4 or 5 per group). Rats in the restraint group were maintained in standard restraint cages. Core temperatures were completed by a YSI series probe (inserted 4 inches into rectum) and Model 46 TUC tele-thermometer approximately 19 hr. later. The ambient room temperature ($M = 21.1°$, *SD* 1.0° C) was not significantly different between groups ($F_{1,18} = 0.32$, $p > .05$).

Analysis of variance, executed by SPSS^X on a VAX 4000 computer, indicated that all of the main effects, two-way interactions, and three-way

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interaction were statistically significant ($F_{1,26}$s > 16.00; range 16.60 to 77.66; $p < .001$). The means and standard deviations of the core temperature for the group in which seizures had been induced and had received restraint and acepromazine was 24.4° C (3.6°) while the group that had been seizured and received the acepromazine only (no restraint) was 34.4° C (1.9°). The temperatures of the rats in each of the six other combinations ranged between 36.4° C (0.5°) and 37.9° C (1.5°).

Post hoc analyses from a one-way analysis of variance for all 8 groups ($F_{7,26} = 33.94$, $p < .001$) indicated that the major effect was between the seizured-restraint-acepromazine group compared to all other groups. The temperatures for the seizured-acepromazine group were significantly different from the no seizure-no restraint-no acepromazine, no seizure-no restraint-acepromazine and no seizure-restraint-no acepromazine groups. The *eta* for the main effect was 0.95.

These results indicated a strong synergism among limbic seizures, restraint, and acepromazine upon core temperature that was evident 19 hr. later. Because acepromazine is essential for survival (Bureau & Persinger, 1992) following the limbic-seizure induction, these results imply that the lowered body temperature may mediate survival. Inferential and experimental work concerning the role of acepromazine on dopaminergic (D1) receptors within the central nucleus of the amygdala, its role in restraint-induced changes, and its unusual integrity when all other amygdaloid nuclei are compromised by the seizure suggest a possible neurological substrate.

Histopathological analyses of the brains of rats in which lithium-pilocarpine seizures were induced suggest maximum damage within MacLean's (1990) phylogenetically newer thalamocingulate pathways. Females with this damage display a complete absence of the distinct behaviors, such as maternal activity (Peredery, Persinger, Blomme, & Parker, 1992), that differentiate mammals from prototypical reptiles. In this context the extreme reduction in core temperature and its significant association with ambient room temperature suggest that the synergistic treatment induced poikilothermia (ectothermia).

These results may be relevant to treatment during the initial hours that follow traumatic brain injury (Hayes, Lyeth, & Jenkins, 1989). That subclinical limbic seizures occur frequently following a brain injury is suspected because this region has an extremely low seizure threshold and has marked susceptibility to mild alterations in the microchemical environment. The occasional generalization to tonic-clonic convulsions, which is both expected and observed, would represent the extreme manifestation of this excitotoxic subclinical limbic process. As many as 35% of patients who are given cardiopulmonary resuscitation (which implies antecedent cerebral hypoxia) display subsequent convulsions (Krumholz & Stern, 1984).

Since rats that display hypothermia (acepromazine and physical restraint) always survive the status epilepticus, there are important implications for human settings. First, the NMDA (n-methyl-d-aspartate) antagonists (such as MK-801 or ketamine variants), that allegedly reduce hypoxia-induced neuronal death following heart attack or stroke (Faden, Demediuk, Panter, & Vink, 1989), are also associated with mild hypothermia. Decreases of core temperature of only 2° to 4° C appear to attenuate the excitotoxic process (Buchan & Pulsinelli, 1990); we found a protracted decrease of at least 10° C but without obvious complication from extreme cardiac arrhythmias.

Secondly, the classic medical response is to prevent hypothermia by wrapping the patient. The extent and pressure is often similar to the physical restraint used in this study. Although physical restraint is considered a necessary artifact of maintaining warmth, this restrictive process may also elicit neurochemical changes that affect neuronal vulnerability during trauma. The history of medicine is replete with procedures that were empirically effective despite periodic revision of the explanation for their effectiveness.

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